Gadolinium Distribution in Cerebrospinal Fluid after Administration of a Gadolinium-based MR Contrast Agent in Humans

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Abstract: Purpose To evaluate whether gadolinium penetrates human cerebrospinal fluid (CSF) after MR imaging (MRI) with a gadolinium-based contrast agent (GBCA). Materials and Methods For this retrospective study, the authors analyzed 60 CSF samples from 57 patients (median age, 50 years; range, 3-92 years) who underwent one contrast material-enhanced MRI examination with gadoterate meglumine within 60 days of CSF extraction between January and December 2016. CSF samples from patients who underwent MRI without contrast material administration (n = 22) or those who underwent contrast-enhanced MRI at least 1 year before extraction (n = 2) were analyzed and used as control samples. CSF measurements were performed with inductively coupled plasma mass spectrometry by monitoring the gadolinium 158 isotope. Statistical analyses were performed by using a preliminary Kruskal-Wallis test. Results Higher CSF gadolinium concentrations were detected within the first 8 hours after GBCA administration (mean concentration, 1152 ng/mL ± 734.6). Concentrations were lower between 8 and 48 hours (872 ng/mL ± 586). After 48 hours, gadolinium was almost completely cleared from CSF (121 ng/mL ± 296.3). All but two samples from the 24 control patients (median age, 60.5 years; range, 19-79 years) were negative for the presence of gadolinium. Those samples were from patients who had undergone GBCA-enhanced MRI examination more than a year before CSF extraction (0.1 and 0.2 ng/mL after 1 and 3 years, respectively). The concentrations in patients with chronic renal insufficiency (n = 3), cerebral toxoplasmosis (n = 1), and liver cirrhosis (n = 1) were higher than the mean concentrations. Conclusion Gadoterate meglumine can be detected in human CSF after intravenous administration.

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Materials and Methods: For this retrospective study, the authors analyzed 60 CSF samples from 57 patients (median age, 50 years; range, 3–92 years) who underwent one contrast material–enhanced MRI examination with gadoterate meglumine within 60 days of CSF extraction between January and December 2016. CSF samples from patients who underwent MRI without contrast material administration (n = 22) or those who underwent contrast-enhanced MRI at least 1 year before extraction (n = 2) were analyzed and used as control samples. CSF measurements were performed with inductively coupled plasma mass spectrometry by monitoring the gadolinium 158 isotope. Statistical analyses were performed by using a preliminary Kruskal-Wallis test.

Results: Higher CSF gadolinium concentrations were detected within the first 8 hours after GBCA administration (mean concentration, 1152 ng/mL ± 734.6). Concentrations were lower between 8 and 48 hours (872 ng/mL ± 586). After 48 hours, gadolinium was almost completely cleared from CSF (121 ng/mL ± 296.3). All but two samples from the 24 control patients (median age, 60.5 years; range, 19–79 years) were negative for the presence of gadolinium. Those samples were from patients who had undergone GBCA-enhanced MRI examination more than a year before CSF extraction (0.1 and 0.2 ng/mL after 1 and 3 years, respectively). The concentrations in patients with chronic renal insufficiency (n = 3), cerebral toxoplasmosis (n = 1), and liver cirrhosis (n = 1) were higher than the mean concentrations.

Conclusion: Gadoterate meglumine can be detected in human CSF after intravenous administration.

For more than 20 years, gadolinium-based contrast agents (GBCAs) have been a cornerstone of clinical MR imaging (MRI) examinations (1,2). Since the initial approval of these agents in the 1980s, they have been considered stable agents with an excellent safety profile at recommended dosage levels (2,3).

In 2005 and 2006, researchers described a correlation between the repeated and cumulative administration of GBCAs and the development of a potentially life-threatening disease, nephrogenic systemic fibrosis, in patients with impaired renal function (4,5). In 2013, Kanda et al (6) described a correlation between GBCA administration and hyperintensity on unenhanced T1-weighted MR images in the globus pallidus and the dentate nucleus in patients with a history of multiple GBCA-enhanced MRI examinations. Since then, a variety of clinical and animal studies have shown that this signal hyperintensity on T1-weighted images is associated with serial injections of linear and rarely macrocyclic GBCAs (1,7–11). Subsequent histopathologic autopsy studies with inductively coupled plasma mass spectrometry (ICP-MS) confirmed brain gadolinium deposition in subjects who underwent GBCA-enhanced MRI examination with either a linear or a macrocyclic GBCA (12–14).

Safety concerns regarding the retention of gadolinium in the brain have consequently emerged (3,15). The U.S. Food and Drug Administration has recommended that health care professionals reassess the necessity of repetitive GBCA-enhanced MRI examinations in established treatment protocols in order to reduce the potential for gadolinium accumulation (16). In addition, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has recently recommended suspension or limitation of the marketing authorizations for four linear GBCAs (17).

The underlying mechanism of the initial pathway and subsequent deposition of GBCAs in the brain has not yet been identified. As a potential pathway for GBCA entry into the brain, GBCA penetration from the blood into the cerebrospinal fluid (CSF) was recently examined in an animal study in healthy rats (7). Our hypothesis was that GBCA penetration into the CSF also occurs in humans. This study was performed to corroborate our hypothesis and evaluate whether gadolinium can be detected in human CSF after GBCA-enhanced MRI.

Abbreviations

CSF = cerebrospinal fluid, GBCA = gadolinium-based contrast agent, ICP-MS = inductively coupled plasma mass spectrometry, IQR = interquartile range

Summary

After contrast-enhanced MRI examination, gadoterate meglumine can easily penetrate into cerebrospinal fluid and is cleared from cerebrospinal fluid over time.

Implications for Patient Care

- Gadoterate meglumine, a macrocyclic gadolinium-based contrast agent, can penetrate into human cerebrospinal fluid (CSF) after intravenous administration.
- CSF gadolinium concentration increases within the first 8 hours after intravenous contrast agent administration and then decreases between 8 and 48 hours.
- Gadoterate meglumine was almost completely cleared from the CSF after 48 hours.

Materials and Methods

Study Design

Our institution received an unrestricted research grant from Guerbet Imaging Switzerland. The company was not involved in our study design, data collection, data analysis, interpretation, or manuscript preparation. In our retrospective study, we performed a comprehensive review of our institute's health care databases, digital medical files, and patient histories to obtain a complete list of all patients who had undergone lumbar puncture and previous GBCA-enhanced MR image acquisition in 2016. Data analysis was performed by two radiologists (R.A.K., with 25 years of experience in clinical radiology, and F.B., with 4 years of experience in clinical and forensic radiology). The focus of our study was the macrocyclic GBCA gadoterate meglumine because of the high prevalence of its use in our institution and in Switzerland. Patients from our outpatient department who had undergone contrast material–enhanced MRI examinations with a different GBCA were rarely seen in our emergency ward and did not undergo lumbar puncture. Our study was approved by the local ethics committee, which authorized the use of CSF samples from 2016 (project identification: 2016-02168). No power calculations were performed because the aim of our study was to prove a hypothesis and basic data for assumption of the effect size were not available.

Participants

Included were all patients in our institution who underwent lumbar puncture between January and December 2016 and one previous MRI examination with the macrocyclic GBCA gadoterate meglumine (at a dose of 0.1 mmol per kilogram body weight) up to 60 days before CSF extraction. For each patient, we performed a comprehensive review of internal digital medical files to obtain a complete GBCA history and a complete patient questionnaire form from previous MRI examinations. Patients were excluded if there was inconclusive history and unknown time of GBCA application, if they had undergone multiple administrations of gadoterate meglumine, if there were insufficient laboratory results at the time of MR imaging, or if the diagnosis was unclear at the time of patient recruitment. Samples with less than 4 mL of CSF were also excluded to ensure that enough CSF remained for potential clinical repeat analysis.

Exposures and Outcomes

In 2016, 292 lumbar punctures were performed at our institution to exclude any central nervous system disorder; 98 patients had undergone contrast-enhanced MRI with gadoterate meglumine at a dose of 0.1 mmol per kilogram body weight up to 60 days before lumbar puncture. Of these, 38 CSF samples did not fulfill the inclusion criteria and were excluded. The majority of these samples were excluded because of insufficient sample size (n = 27) or multiple administrations of gadoterate meglumine (n = 8) (Fig 1). A total of 60 CSF samples from 57 patients were eventually analyzed in our study. Forty-seven of the 57 participants underwent lumbar puncture because of neurologic disorders. The remaining 10 participants had psychiatric (n = 2), neoplastic (n = 5), or other (n = 3) disorders. For each patient, laboratory results (serum creatinine level, estimated glomerular filtration rate, C-reactive protein level, and aspartate aminotransferase level) at the time of MRI examination were collected from our extended health care network. In total, 28 of the CSF samples showed an elevated total CSF protein count (>0.45 g/L; range, 0.48–2.2 g/L); the remaining CSF samples showed no abnormalities. The CSF samples were divided into three subgroups depending on the time between GBCA administration and CSF extraction, as follows: subgroup 1 (n = 31), 0–8 hours; subgroup 2 (n = 13), 8–48 hours; and subgroup 3 (n = 16), 2–60 days.

Twenty-four patients were enrolled in a control group. Of these, all but one patient had neurologic disorders, including cerebrovascular insult, paresthesia, Guillain-Barré syndrome, syncope, peripheral facial paralysis, and meningitis. The other patient was diagnosed with B-cell lymphoma. Of the 24 patients in the control group, 22 had not undergone MRI or had undergone unenhanced MRI and two had undergone GBCA-enhanced MRI at least 1 year before CSF extraction (1 and 3 years, respectively), as recorded in our medical files. All other inclusion criteria were the same as for the GBCA group. All patients in the contrast and control groups lived within the canton of Aargau, Switzerland, and received the majority of their health care at our medical center or within our extended health care network, which permitted access to their previous radiologic examinations. Most CSF samples in the control group (n = 17) showed no abnormalities. The total CSF protein count in the remaining seven CSF samples was greater than 0.45 g/L (range, 0.52–1.04 g/L).

Determination of CSF Total Gadolinium Concentration

Sample preparation for ICP-MS.—All CSF samples were anonymized. The laboratory staff was blinded to group allocation and had no access to the study data. Sample analysis was performed by an experienced forensic toxicologist (M.P., with 7 years of experience in forensic pharmacology and toxicology). A 0.3-mL aliquot

of the sample was diluted with ultrapure water to 3.0 mL. All calibration standard solutions were prepared from 1 mg/mL single-element standard solutions (Merck, Darmstadt, Germany) by means of dilution with ultrapure water.

Performance of ICP-MS.—An Analytik Jena PlasmaQuant MS instrument (Analytik Jena, Jena, Germany) in the highest stage of completion (Elite version), equipped with a type 142 Varian cooler and a Varian SPS 3 Autosampler (Varian, Darmstadt, Germany), was used for quantification of gadolinium isotopes. with the following measurement parameters: analysis type: quantitative; acquisition mode: steady state; scan mode: peak hopping; spacing, coarse, points per peak: I; scans per replicate: 20; replicates per sample: 3; plasma: plasma flow, 7.50 L/min; auxiliary flow: 1.40 L/min; sheath gas flow: 0.00 L/min; nebulizer flow: 0.99 L/min; sampling depth: 5.00 mm; ion optics (volt): skimmer bias, 0.00; first extraction lens: −70.00; second extraction lens: −306.00; third extraction lens: −370.00; left mirror lens: 60.00; right mirror lens: 31.00; bottom mirror lens: 37.00; corner lens: −318.00; entrance lens: 3.00; fringe bias: −4.50; entrance plate: −96.00; collision reaction interface: skimmer cone, helium; skimmer gas flow: 80 mL/min; sampling: aerosol generation, nebulizer; source: autosampler; fast pump during sample delay and rinse: on; rinse time: 40 seconds; spray chamber temperature: 3.00°C; sample uptake delay: 60 seconds; scanning time: 181 minutes; and replicate time: 3.62 seconds. Gadolinium isotopes 152, 154, 155, 156, 157, 158, and 160 were measured, and gadolinium 158 (^{158}Gd) was used for quantification.

All chemicals and materials were checked for interferences. Calibration was performed for every series by using standard solutions of 0.01, 0.1, 1, and 10 μg gadolinium per liter and a blank sample. The aforementioned calibration range samples were diluted and measured again to fit to the calibration range. Dotarem production samples (Guerbet, Zurich, Switzerland) containing 0.5 mmol of gadolinium per milliliter were used as external controls and analyzed before and after a measurement series.

Statistical Analysis

Statistical analyses were performed by two readers (F.B. and T.K., with 29 years of experience in clinical and forensic pharmacology and toxicology). For statistical analysis of the data (Grubbs outlier test, Kruskal-Wallis test), software was used (GraphPad Prism 6 [GraphPad Software, La Jolla, Calif] and R, version 3.1.0 [R Foundation for Statistical Computing, Vienna, Austria]). Continuous variables are presented as medians, interquartile ranges (IQRs), and ranges, owing to nonnormal data distributions, unless otherwise noted. Comparison of all four groups (three subgroups and the control group) was performed by using a preliminary Kruskal-Wallis test with post hoc correction at $\alpha = .05$. Significance was assigned to differences with $P \leq .05$.

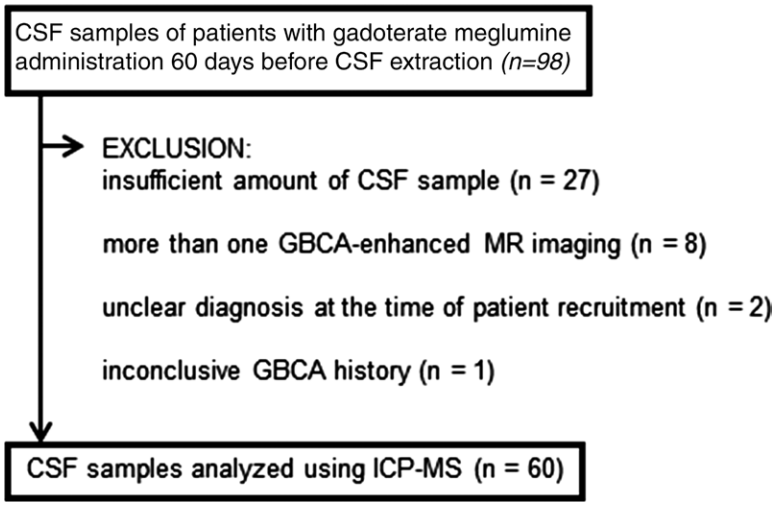

Figure 1: Flowchart shows formation of study group with exclusion criteria. *CSF* = cerebrospinal fluid, *GBCA* = gadolinium-based contrast agent, *ICP-MS* = inductively coupled plasma mass spectrometry.

Results

Determination of CSF Total Gadolinium Concentrations

Reliable quantification of gadolinium in CSF samples was easily achieved with ICP-MS. Simple dilution of the CSF samples with ultrapure water was sufficient for achievement of interference-free (tested with blank samples) measurements. Linearity (given as R^2) was always better than 0.9995. All stable gadolinium isotopes (^{152}Gd, ^{154}Gd, ^{155}Gd, ^{156}Gd, ^{157}Gd, ^{158}Gd, and ^{160}Gd) were measured, and the ^{158}Gd isotope was used for quantification. In positive cases, measurement of the other gadolinium isotopes led to almost identical results (<10% difference). The external controls, measured before and after each series, did not show any drift in results.

Patient Populations

A total of 60 CSF samples from 57 patients (29 female and 28 male patients) were analyzed. The median age of patients in the contrast group was 50 years (range, 3–92 years). The contrast group was divided into subgroups on the basis of the interval between GBCA administration and CSF extraction, as follows: subgroup 1, 0–8 hours; subgroup 2, 8–48 hours; and subgroup 3, 2–60 days. The median age of the patients in subgroup 3 at the time of MRI examination (68 years [IQR, 43.5–78.5 years]) was higher than that in subgroup 1 (48 years [IQR, 28–59 years]; $P = .04$), subgroup 2 (48 years [IQR, 36–73 years]; $P = .48$), and the control group (60.5 years [IQR, 50.5–67.8 years]; $P = .56$). In the contrast group, three male patients had undergone two lumbar punctures after GBCA-enhanced MRI examination: at 2.3 hours and 5.4 days after examination, at 7.3 and 21.5 hours after examination, and at 5.0 and 11.3 days after examination, respectively.

Gadolinium was detected in all CSF samples from the contrast group, with an overall mean concentration (±standard

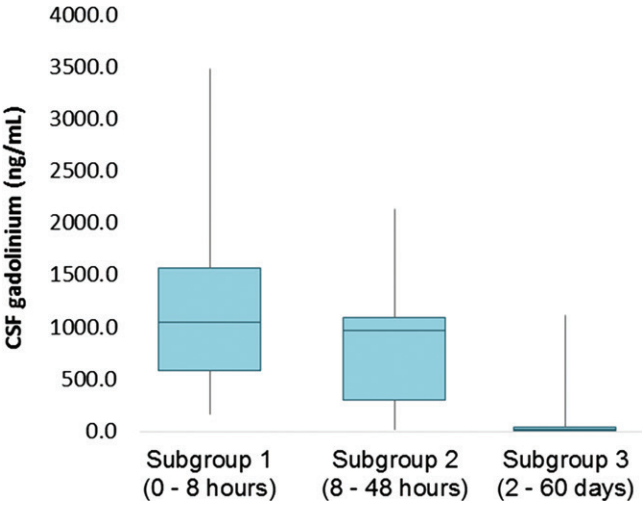

Figure 2: Box plot shows gadolinium levels measured in cerebrospinal fluid (CSF) with inductively coupled plasma mass spectrometry and decrease of CSF gadolinium concentration over time.

deviation) of 816.1 ng/mL ± 746.6 (range, 0.1–3481.9 ng/mL). A comparison of median values and ranges in the three subgroups can be seen in Figure 2. There was no difference in gadolinium concentration between female and male patients (P = .91). Furthermore, the independent variables of liver function and inflammatory parameters did not influence the CSF gadolinium concentration (P = .77 and P = .39, respectively).

In subgroup 1 (n = 31 samples), CSF gadolinium concentration ranged from 167.9 to 3481.9 ng/mL, with a mean concentration of 1151.5 ng/mL ± 734.6. The median interval between GBCA administration and CSF extraction was 4.6 hours (IQR, 3.3–5.3). As shown in Table 1, the main diagnoses in this group were as follows: neurologic disorders (n = 29), psychiatric diseases (n = 1), and others (n = 1). Statistical analysis with the Grubbs test identified the highest gadolinium concentration of 3481.9 ng/mL in a female patient with newly diagnosed human immunodeficiency virus infection with cerebral toxoplasmosis as an outlier. Most patients in subgroup 1 had an estimated glomerular filtration rate greater than 60 mL/min/1.73 m^2. Only two patients had a lower estimated glomerular filtration rate (45 and 20 mL/min/1.73 m^2) and CSF gadolinium concentrations that were higher than the mean concentration (1945 and 2256.7 ng/mL). In subgroup 1, the only patient with liver cirrhosis also had a gadolinium concentration that was among the highest (2211.5 ng/mL 6.3 hours after GBCA administration).

Concentrations in subgroup 2 (n = 13 samples) ranged from 17.8 to 2140.7 ng/mL, with a mean concentration of 871.7 ng/mL ± 586.1. The median interval between GBCA-enhanced MRI examination and lumbar puncture was 23.4 hours (IQR, 8.9–26.5). The main diagnoses were neurologic disorders (n = 9), psychiatric diseases (n = 1), neoplastic disorders (n = 2), and other diagnosis (n = 1) (Table 2). Compared with the other subgroups and the control group, subgroup 2 showed a higher median C-reactive protein level (8.0 mg/L [IQR, 2.0–17.0 mg/L]) and aspartate aminotransferase level (31.0 U/L [IQR, 20.0–47.0 U/L]), although the differences were not statistically significant (P = .64 and P = .84, respectively).

In subgroup 3 (n = 16 samples), the mean CSF gadolinium concentration was 121 ng/mL ± 296.3 (range, 0.1–1118.8 ng/mL). The median interval between GBCA administration and CSF extraction was 5.7 days (IQR, 3.2–11.8 days). The main diagnoses in subgroup 3 were neurologic disorders (n = 12), neoplastic disorders (n = 3), and chronic renal failure (n = 1) (Table 3). The gadolinium concentration 3 days after GBCA administration was higher in a patient with chronic renal failure (531.7 ng/mL) compared to the two patients whose samples were obtained 3.2 days after MRI examination (44.0 and 19.0 ng/mL, respectively).

A 21-year-old male patient with viral meningoencephalitis underwent lumbar punctures at 2.3 hours and 5.4 days after GBCA administration and showed a clear decrease in gadolinium concentration, from 522 to 1.9 ng/mL, during the 5-day period. The other two patients with two lumbar punctures showed a similar decrease from 1885 to 1508.2 ng/mL (at 7.3 and 21.5 hours) and from 43.9 to 1.9 ng/mL (at 5.0 and 11.3 days), respectively.

In the control group, all samples were negative for the presence of gadolinium except the two CSF samples from the patients who had undergone a GBCA-enhanced MRI examination more than a year before CSF extraction. These samples had gadolinium concentrations of 0.1 and 0.2 ng/mL in CSF after 1 and 3 years, respectively.

Discussion

The results of our study confirm the presence of gadolinium in human CSF after MRI with the macrocyclic GBCA gadoterate meglumine and demonstrate a decrease in CSF gadolinium concentration over time. Higher CSF gadolinium concentrations were detected within the first 8 hours after GBCA administration (mean concentration, 1152 ng/mL ± 735), whereas the gadolinium concentrations were lower between 8 and 48 hours (mean concentration, 872 ng/mL ± 586) and after 48 hours (mean concentration, 121 ng/mL ± 296).

Previous studies showed that a higher signal intensity can be detected with MRI in various cranial fluid spaces after the administration of a GBCA (18–21). Naganawa et al (20,21), for instance, detected contrast enhancement in CSF and perivascular spaces with heavily T2-weighted three-dimensional fluid-attenuated inversion-recovery MRI after intravenous GBCA administration, a finding that suggests GBCA penetration into cranial fluids. We confirmed these early findings by using an absolute gadolinium detection method (ICP-MS) rather than simply inferring the presence of gadolinium by means of elevated signal intensities.

In their study in healthy rats, Jost et al (7) demonstrated that both linear and macrocyclic GBCAs are almost completely cleared from CSF within 24 hours. Our results are in accordance with the findings of this preclinical study and demonstrated an almost complete clearance of gadoterate meglumine from CSF 48 hours after administration. In the contrast groups, the elimination of gadoterate meglumine from CSF is further shown in the decrease in gadolinium concentration over time in the CSF samples of three male patients with two subsequent lumbar punctures.

Gadolinium could be detected even in subjects with a presumably intact blood-brain barrier. This suggests GBCA penetration

Table 1: Characteristics of Patients in Subgroup 1

Age (y)/Sex	Major Diagnosis	eGFR (mL/min/1.73 m^2)	CRP Level (mg/L)	AST Level (U/L)	Interval between GBCA Administration and Lumbar Puncture (h)	Gd CSF Concentration (ng/mL)
50/F	Tension headache	>60	1	23	4	974.4
73/M	Erysipelas of the foot	>60	10	39	5.5	1447.1
35/M	Paresthesia	>60	1	25	2.6	1159.8
77/F	Generalized epileptic seizure	45	48	53	5.2	1945.0
58/M	Nonconvulsive epileptic seizure	>60	70	14	3.6	1272.3
78/M	Peripheral facial paralysis	>60	1	40	3.3	953.9
74/F	Hemichorea-hemiballismus	>60	3	32	5.4	838.6
54/M	Acute polyneuropathy	>60	2	21	6.1	1962.1
25/F	Generalized epileptic seizure	>60	2	23	5.1	1001.6
19/M	Acute psychosis	>60	1	61	2.2	210.4
20/F	Sepsis	>60	18	25	3.6	167.9
49/F	Clinically isolated syndrome	>60	10	31	4.8	1084.1
33/M	Clinically isolated syndrome	>60	2	24	5.8	1700.4
33/M	Viral meningoencephalitis	>60	17	28	5.2	1251.4
51/F	Migraine	>60	1	81	3.3	649.3
54/F	Flu	>60	117	13	5.2	967.8
28/F	Steroid-induced encephalopathy	>60	11	27	3.4	388.0
43/M	Vertigo	>60	1	25	5.1	922.7
3/F	Streptococcal infection	>60	1	13	1.1	171.3
21/M	Viral meningoencephalitis	>60	6	18	2.3	522.0
60/F	Generalized epileptic seizure, chronic kidney failure	20	7	29	5.6	2256.7
28/F	Intracranial toxoplasmosis, human immunodeficiency virus infection	>60	1	16	3.2	3481.9
73/M	Cerebrovascular insult	>60	1	15	4.9	1746.0
26/M	Viral meningoencephalitis	>60	1	26	1.4	1052.2
92/M	Focal epileptic seizures	>60	25	27	7.3	1885.0
30/F	Tension-type headache	>60	1	32	5.9	480.4
48/M	Migraine	>60	1	24	4.6	441.3
31/F	Nocturnal paresthesia	>60	1	26	4.3	1062.2
60/F	Liver cirrhosis	>60	2	21	6.3	2211.5
4/F	Flu	>60	53	38	3.4	433.8
52/M	Chronic Lyme disease	>60	1	124	2.7	1054.3

Note.—Subgroup 1 had an interval of 0–8 hours between gadolinium-based contrast agent (GBCA)–enhanced MR imaging and cerebrospinal fluid (CSF) extraction. AST = aspartate aminotransferase (normal laboratory range for assay, 10–35 U/L), CRP = C-reactive protein (normal laboratory range for assay, 0.1–5 mg/L), eGFR = estimated glomerular filtration rate (normal laboratory range for assay, >60 mL/min/1.73 m^2), Gd CSF = gadolinium concentration in CSF measured with inductively coupled plasma mass spectrometry.

into CSF regardless of blood-brain barrier permeability. This is in accordance with a recent observation by McDonald et al (22) that gadolinium deposition in neural tissue occurs even in the absence of intracranial abnormalities that affect the blood-brain barrier. Future studies should focus on the influence of cranial lesions and blood-brain barrier disruptions on CSF gadolinium concentrations.

In our study subgroups, CSF levels of gadolinium in patients with chronic renal insufficiency tended to be among the highest (2257, 2140, and 532 ng/mL after 5.5 hours, 25.5 hours, and 3 days after MRI, respectively), indicating a prolonged GBCA elimination from CSF. Furthermore, the outlier test revealed one case of newly diagnosed human immunodeficiency virus infection and central nervous system toxoplasmosis with significantly higher CSF gadolinium concentrations (3482 ng/mL 3.2 hours after MRI), a finding that suggests that the blood-CSF barrier is more permeable in patients with acute cerebral infections. Both observations must be verified in future studies focusing on the influence of renal insufficiency and cerebral infections on GBCA penetration and elimination.

In the control group, two CSF samples were taken from patients who had undergone enhanced MRI examination 1 and 3 years prior to lumbar puncture, respectively. In those samples, traces of gadolinium could still be detected, whereas all other control samples were negative. It is unclear whether these findings indicate an actual long-term intracranial GBCA deposition. If GBCAs were retained in CSF or in the brain, it can be

Table 2: Characteristics of Patients in Subgroup 2

Age (y)/Sex	Major Diagnosis	eGFR (mL/min/1.73 m²)	CRP Level (mg/L)	AST Level (U/L)	Interval between GBCA Administration and Lumbar Puncture (h)	Gd CSF Concentration (ng/mL)
36/F	Paresthesia	>60	1	25	8.5	967.0
31/F	Migraine	>60	16	84	7.7	1073.0
51/M	Generalized epileptic seizures	>60	1	16	8.9	1098.2
51/M	Cerebrovascular insult	>60	1	37	8.9	1098.0
26/F	Migraine	>60	34	20	19.65	1081.1
92/M	Focal epileptic seizure	>60	25	124	21.5	1508.2
46/F	Schizophrenia	>60	3	38	23.4	184.7
85/M	Chronic renal failure	51	17	91	25.4	2140.7
73/M	B-cell lymphoma	50	2	31	26	869.5
74/F	Cerebrovascular insult	>60	74	47	26.5	722.3
47/F	Paresthesia	>60	13	14	27.8	267.2
61/F	Paraneoplastic syndrome	>60	1	21	44.4	304.2
28/F	Clinically isolated syndrome	>60	8	20	45.1	17.8

Note.—Patients in subgroup 2 underwent lumbar puncture 8–48 hours after gadolinium-based contrast agent (GBCA)–enhanced MR imaging. AST = aspartate aminotransferase (normal laboratory range for assay, 10–35 U/L), CRP = C-reactive protein (normal laboratory range for assay, 0.1–5 mg/L), eGFR = estimated glomerular filtration rate (normal laboratory range for assay, >60 mL/min/1.73 m²), Gd CSF = gadolinium concentration in CSF measured with inductively coupled plasma mass spectrometry.

Table 3: Characteristics of Patients in Subgroup 3

Age (y)/Sex	Major Diagnosis	eGFR (mL/min/1.73 m²)	CRP Level (mg/L)	AST Level (U/L)	Interval between GBCA Administration and Lumbar Puncture (d)	Gd CSF Concentration (ng/mL)
75/F	Cerebral metastases	>60	4	110	2.0	1118.8
21/F	Migraine	>60	1	20	2.8	15.0
36/M	Hypoxic encephalopathy	>60	2	35	3.0	44.0
86/F	Chronic renal failure	42	4	19	3.2	531.7
52/F	Syncope	>60	2	39	3.2	19.0
41/M	Acute motor axonal neuropathy	>60	2	25	4.2	21.2
77/M	Viral meningoencephalitis	>60	17	18	5.0	43.9
21/M	Viral meningoencephalitis	>60	6	13	5.4	1.9
60/M	Vasculitis	58	3	25	6.0	16.6
80/M	Normal pressure hydrocephalus	>60	3	26	6.0	106.0
84/M	Viral meningoencephalitis	>60	6	34	7.0	11.1
77/M	Viral meningoencephalitis	>60	17	18	11.3	4.8
46/M	Viral meningoencephalitis	>60	22	34	13.1	0.3
70/F	Cerebral metastases	>60	1	23	50.1	0.1
68/M	B-cell lymphoma	>60	4	40	27.0	0.3
83/M	Unclear ataxia	>60	1	29	17.1	1.8

Note.—Patients in subgroup 3 underwent lumbar puncture 2–60 days after gadolinium-based contrast agent (GBCA)–enhanced MR imaging. AST = aspartate aminotransferase (normal laboratory range for assay, 10–35 U/L), CRP = C-reactive protein (normal laboratory range for assay, 0.1–5 mg/L), eGFR = estimated glomerular filtration rate (normal laboratory range for assay, >60 mL/min/1.73 m²), Gd CSF = gadolinium concentration in CSF measured with inductively coupled plasma mass spectrometry.

assumed that they circulate among blood, CSF, brain, and other body tissues in constant equilibrium. Therefore, it can be argued that the gadolinium concentration detected in CSF by means of ICP-MS probably represents the GBCA remaining in all body tissues.

The mechanism of GBCA accumulation in the brain is still unknown. Jost et al (7) discussed the involvement of CSF in the entry of GBCAs into the brain. More recently, the glymphatic system has been discussed as a potential pathway for GBCA entry into the brain (23). The glymphatic system is a paravascular pathway for CSF and interstitial fluid exchange in the brain and might play a role in residual gadolinium deposition (23,24).

Our study had some limitations, including the assessment of only one GBCA. Further work must be performed to investigate

the kinetics of gadolinium in CSF across various approved GBCAs. Because only internal medical databases and patient questionnaire forms were screened to obtain each patient's MRI history, it is possible that previous external MRI examinations may have influenced CSF gadolinium concentrations. Owing to the limited number of subjects, we could not evaluate the relationship of gadolinium concentrations between patients with and patients without brain lesions. There was a high exclusion rate of 38 samples; most of these (n = 27) were excluded because of the limited amount of CSF available in the sample.

In conclusion, our findings substantiate those of recent studies indicating that the macrocyclic GBCA gadoterate meglumine easily penetrates into CSF regardless of renal function and in patients with a presumably intact blood-brain barrier. More important, our findings suggest that this GBCA is almost completely eliminated 48 hours after intravenous administration. Although we examined the CSF penetration of only one type of GBCA, our findings strongly argue for future research to assess the pharmacokinetics and penetration into CSF of other GBCAs in conjunction with central nervous system lesions.

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